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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,326	03/20/2006	Stan Gronthos	75191/JPW/JW	6525

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EXAMINER	
HIRIYANNA, KELAGINAMANE T	
ART UNIT	PAPER NUMBER
1633	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,326	GRONTHOS ET AL.	
	Examiner	Art Unit	
	KELAGINAMANE T. HIRIYANNA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *131-191* is/are pending in the application.

4a) Of the above claim(s) *131-171,173,174 and 182* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *172,175-181 and 183-191* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/06 ,08/07, 04/08, 10/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Restriction of invention

Applicant's election of Invention III (Claims 172, 175-181 and 183-191, drawn to a method of inducing formation of blood vessels comprising administering a cultured or expanded enriched population of cells that express the marker Stro-1) with traverse of restriction requirement in the reply filed on October 06, 2008 is acknowledged. The Applicant traverses on the grounds that there is no serious burden on the examiner to examine all the species in the claims. The Applicants arguments are however, found not persuasive because the invention as claimed in claims 131-191 broadly encompass inducing the formation or repair of blood vessels in any tissue using MPCs from different sources and niches and enriched to different extents and with reference to different combination of markers. The claims further encompass treating a subject suffering from a disease associated with loss of alpha smooth muscle. Thus searching and examining all the claims in the claims together is a serious burden on the examiner and hence the restriction as indicated is proper and is made final.

Claims 187-191 are currently added to the elected invention III as they are amended by the Applicant in the response of October 06, 2008 to depend directly or indirectly from the base claim 172.

Claims 131-171, 173-74 and 182 are withdrawn from further consideration.

Claims 172, 175-181 and 183-191 are pending and presently under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention."

Claims 172, 175-181 and 183-191 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inducing neovascularization at the site of administration by a direct injection of isolated mesenchymal precursor cells (MPCs) from bone marrow cells that express STRO-1,

does not enable any neovascularization by administering or contacting said cells from any tissue source to a target tissue and administering by any route or therapy of any disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims as explained below.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the prior art; (4) The level of one of ordinary skill; (5) The level of predictability in the art; (6) The amount of direction provided by the inventor; (7) The existence of working examples; and (8) The quantity of experimentation needed to make or use the invention based of the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). All of the wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below as to show that one of the ordinary skill in the art have to go through "undue experimentation" in order to practice the invention.

Nature of the invention and the breadth of the claims: The claims are broadly drawn to a method of inducing formation of blood vessels by administering via any route an enriched population of isolated and cultured cells that express the marker STRO-1 wherein in further limitations the cells used in such a therapy express STRO-1 are mesenchymal precursor cells (MPCs) that are enriched to variable extent, comprise additional markers 3G5, MUC18/CD46 and/or alpha smooth muscle actin and/or negative for certain other markers, derived from several different tissue sources(and encompassing autologous or allogenic or xenogenic sources), isolated from different niches from a tissue and preferably from perivascular niche, that administration of said cells induce new blood vessel structures etc. The nature of the invention is such that one of ordinary skill in the art would find it "undue experimentation" without a sufficient guidance in the form of prior art teachings and/or by a sufficient guidance in the as filed specification.

The level of one of ordinary skill in the Art at the Time of Invention: The level of one of ordinary skill in the art at the time of filing of the instant application is high requiring an advanced degree or training in the relevant field. The status of the art at the time of filing was such that said skilled in the art would not have been able to make or use the invention for its fully claimed scope without "undue experimentation".

***Guidance of the Specification and the Existence of Working Examples*:** The specification as filed teaches in passing only regarding the induction of arterioles at the site of injection of said cells to tumor transplants or hearts of athymic nude rats (paragraph 0137-0140) primarily using MPCs derived from bone marrow. As filed specification primarily focuses only on methods of isolation of Stro-1+ MPCs from dental pulp and bone marrow and an histochemical analysis of the perivascular niche occupied by said Stro-1 positive CD146 positive MPCs in various animal tissues.

The specification however, does not provide any evidence for the formation of arteries, veins and capillaries (neo-vascularization) formed as a result of administering said Stro+ cells. The indicated Figures 1, 2. 3, 4 supposed to support the teachings in paragraphs 0147-0148 are completely inconsistent with the reported observations discussed therein. Further the specification as filed does not provide sufficient number enabled examples that support the broad claim to using MPCs from a laundry list of animal tissue sources in claim 184. In the absence of such enabling disclosures in the as filed specification for the aforementioned broad method claims one of skill in the art the applicant would find it "undue experimentation" to make and use the invention as claimed.

***State of the Art, the Predictability of the Art*:** At about the effective filing date of the present application art teaches of the unpredictability regarding the clinical use of Bone marrow derived stromal cells such as MPCs and MSCs. For example Barry et al (2003, Birth Defect Research (Part C) 69:250-256) states that there are several aspects to the implanted cell-host interaction that need to be addressed in order to understand the mechanism underlying stem cell therapies. These are the (1) the host immune response to implanted cells, (2) the homing mechanisms that guide delivered cell to a site of injury, and (3) differentiation of implanted cells under the influence of local signals

(p.251, col.2 and p.252, 3rd ¶). Further Barry notes the importance of demonstrating safety and efficacy of MSC therapy and indicates that many questions remain to be answered regarding mechanism of action of these cells (p.255, col.2, 3rd ¶). Kassem et al., (2004, Cloning Stem Cells 6:369-74) states that "Before their (widespread use in therapy, methods allowing generation of large number of cells without affecting their differentiation potential as well as technologies that overcome immunological rejection (in case of allogenic transplantation) must be developed". Le Blanc et al (2005, Biology of Blood and marrow transplantation 11:321-334) states that "many questions regarding MSCs cannot be answered today and most of what is known about MSCs is derived from in vitro experiments. When administered in vivo, MSCs have been difficult or almost impossible to detect. Clinical effects of MSCs have clearly been observed; however, it is possible that the effect of MSCs has been due to local production of growth factors rather than to direct participation of MSCs in healing process. Much more work especially in vivo is required to increase our knowledge of how MSCs act and their fate and need to wait for such additional data, because significant effects, albeit anecdotal, have already been noted in the clinic". (p.328, col.2, 2nd paragraph-quote in parts). This unpredictability in art continues to persist as indicated by Summer et al., (2008, Proc. Am, Thorac. Soc 5:707-710: entire article; p.707 col.2) that "There is a general consensus that the field of MSC biology is significantly less developed than other stem cell fields".

Amount of experimentation necessary: These claims are not enabled because one of skilled in the art would not be able to rely upon the state of the art in order to successfully transplant in MSCs or MPCs obtained from any tissue to induce formation of neovascular tissue, and further not be able to trans-differentiate such transplanted cells into the structure of the vascular tissue. Accordingly, in view of the art-recognized unpredictability with regard to transplantation, trans-differentiation, and plasticity of said MSCs (MPCs) and in view lack of teachings in the art regarding a successfully using MSCs/MPCs obtained from the claimed laundry list of tissues for inducing neovascularization and further in view of the scant guidance provided by the specification with regard to an enabled use of MPCs other than from bone marrow

tissue and dental pulp and for the specific reasons cited above, it would have required undue experimentation for one of skill in the art to make and use the full scope of the claimed invention. One of skill in the art has to undertake 'undue experimentation' in order to research for the applicant that any or a sufficient number of tissue sources claimed would provide MPCs that when administered to any tissue would induce and assemble new blood vessels.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 172, 175-181 and 183-191 are rejected under 102(b) as being anticipated by Chopp et al., (2002, The Lancet Neurology 1:92-100).

The above The claims are drawn to a method of inducing formation of blood vessels by administering via any route an enriched population of isolated and cultured cells that express the marker STRO-1 wherein in further limitations the cells used express STRO-1 are mesenchymal precursor cells (MPCs) that are enriched to variable extent, comprise additional markers 3G5, MUC18/CD46 and/or alpha smooth muscle actin and/or negative for certain other markers, derived from several different tissue sources, isolated from different niches from a tissue and preferably from perivascular niche and enriched to different extent with respect to cells possessing said markers.

Regarding claims 172, 175-181 and 183-191 Regarding the claim limitations of vasculogenesis or neovascularisation using MSCs (MPCs) Chopp teaches a method of promoting angiogenesis during a treatment of neural injury with bone marrow stromal cell including mesenchymal stem cells (MSC) following in vivo and systemic administration of said cell in rats (entire article; abstract; p.93, col.1 2nd paragraph

bridging col.2). Chopp further teaches direct implantation, injection as well as systemic administration of said cells including intravenous delivery and effect the recovery from pathological process by regenerative angiogenesis, vasculogenesis (Abstract; p.96-98; Fig.3). Stro-1 marker expression in said MSC is inherent for these fibroblastic bone marrow cells and it was known in the art at the time of invention. Thus the rejected claims are within the scope of the Chopp's anticipation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 172, 175-181 and 183-191 are rejected under 103(c) as being unpatentable over Chopp et al., (2002, The Lancet Neurology 1:92-100) in view of Jones et al (2002, Arthritis and Rheumatism 46:3349-3360)

The above The claims are drawn to a method of inducing formation of blood vessels by administering via any route an enriched population of isolated and cultured cells that express the marker STRO-1 wherein in further limitations the cells used express STRO-1 are mesenchymal precursor cells (MPCs) that are enriched to variable extent, comprise additional markers 3G5, MUC18/CD46 and/or alpha smooth muscle actin and/or negative for certain other markers, derived from several different tissue sources, isolated from different niches from a tissue and preferably from perivascular niche and enriched to different extent with respect to cells possessing said markers.

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injection as well as systemic administration of said cells including intravenous delivery and effect the recovery from pathological process by regenerative angiogenesis, vasculogenesis (Abstract; p.96-98; Fig.3). Stro-1 marker expression in said MSC is inherent for these fibroblastic bone marrow cells and it was known in the art at the time of invention. Chopp however, does not expressly teach various claimed markers on said MSCs or MPCs.

Elena teaches regarding the limitations of various markers on the MSCs (MPCs) in claims 180, 181 and 183. In addition to Stro-1+ (Abstract; p3350, col.1, 2nd paragraph) cells further possess various markers including CD29, CD10, CD13 and were negative for CD34. Elena further teaches regarding expanding these cells in culture and clonal assays (entire article; p.3350, col.1, 3rd paragraph; col.2 2nd paragraph)

Regarding claim limitations of using said MPCs or MSCs at various stages of enrichment in claims 175-179 and 187-191 It is well settled that routine optimization is not patentable, even if it results in significant improvements over the prior art. In support of this position, attention is directed to the decision in *In re Aller, Lacey, and Hall*, 105 USPQ 233 (CCPA 1955):

Normally, it is to be expected that a change in temperature, or in concentration, or in both, would be an unpatentable modification. Under some circumstances, however, changes such as these may impart patentability to a process if the particular ranges claimed produce a new and unexpected result which is different in kind and not merely in degree from the results of the prior art. In re Dreyfus, 22 C.C.P.A. (Patents) 830, 73 F.2d 931, 24 USPQ 52; In re Waite et al., 35 C.C.P.A. (Patents) 1117, 168 F.2d 104, 77 USPQ 586. Such ranges are termed "critical" ranges, and the applicant has the burden of proving such criticality. In re Swenson et al., 30 C.C.P.A. (Patents) 809, 132 F.2d 1020, 56 USPQ 372; In re Scherl, 33 C.C.P.A. (Patents) 1193, 156 F.2d 72, 70 USPQ 204. However, even though applicant's modification results in great improvement and utility over the prior art, it may still not be patentable if the modification was within the capabilities of one skilled in the art. In re Sola, 22 C.C.P.A. (Patents) 1313, 77 F.2d 627, 25 USPQ 433; In re Normann et al., 32 C.C.P.A. (Patents) 1248,

150 F.2d 708, 66 USPQ 308; In re Irmscher, 32 C.C.P.A. (Patents) 1259, 150 F.2d 705, 66 USPQ 314. More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. In re Swain et al., 33 C.C.P.A. (Patents) 1250, 156 F.2d 239, 70 USPQ 412; Minnesota Mining and Mfg. Co. v. Coe, 69 App. D.C. 217, 99 F.2d 986, 38 USPQ 213; Allen et al. v. Coe, 77 App. D. C. 324, 135 F.2d 11, 57 USPQ 136. (Emphasis added).

Further regarding various markers claimed for the MPCs/MSCs and their niche in a tissue (such as bone marrow peri-vascular niche etc) in claims 183-186, the Applicant should note Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir.1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433. See also Titanium Metals Corp. v. Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985)"

Thus it would have been obvious for one of ordinary skill in the art to incorporate into the method of promoting angiogenesis in an organ or tissue by administering MScs/MPC as taught by Chopp a step of confirming the identity of MSCs and MPCs as Stor-1+ cells as taught by Jones and administer in effective amounts of MSCs (or Stro1+ MPCs) to induce neovascularization in a tissue. One of ordinary skill in the art would have been motivated to use MSCs (or Stro-1+ MPCs) in order to promote angiogenesis which in turn may promotes healing of the affected organ by relieving from ischemia. One of ordinary skill in the art would have reasonable expectation of success in making and using enriched MSCs/MPCs with said markers for inducing neovascualrization because the art teaches that it is routine to transplant MSC/MPCs to

a tissue or a transplanted tumor in vivo to induce neovascularization. Thus, the claimed invention was prima facie obvious.

Conclusion

No claim allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Kelaginamane Hiriyanna Ph.D.,* whose telephone number is **(571) 272-3307**. The examiner can normally be reached Monday through Thursday from 9 AM-7 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Joseph Woitach Ph.D.*, may be reached at **(571) 272-0739.** The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). When calling please have your application serial number or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. For all other customer support, please call the USPTO call center (UCC) at (800) 786-9199.

Kelaginamane T. Hiriyanna

Patent Examiner

Art Unit 1633

/Robert M Kelly/

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